

Palliation of nausea and vomiting in malignancy

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Nausea and vomiting are common symptoms that can cause enormous misery for cancer patients, undermining quality of life and contributing to weakness, anorexia and nutritional problems.¹ Evidence-based recommendations for the management of treatment-induced emesis are available, but the management of nausea arising as a consequence of the disease itself is less well researched. This article summarises palliative care guidelines derived from animal models and validated in a range of human studies.^{2,3}

Mechanisms of nausea and vomiting

Emesis is a protective reflex triggered by physical stimuli that include poisoning and overdistension of hollow viscera, psychological stimuli or vestibular stimulation (including motion sickness). The various nerve pathways activated by these stimuli are summarised in Fig 1.⁴

Chemical triggers to nausea are detected at the chemoreceptor trigger zone (CTZ) in the floor of the 4th ventricle. Here, there is effectively no

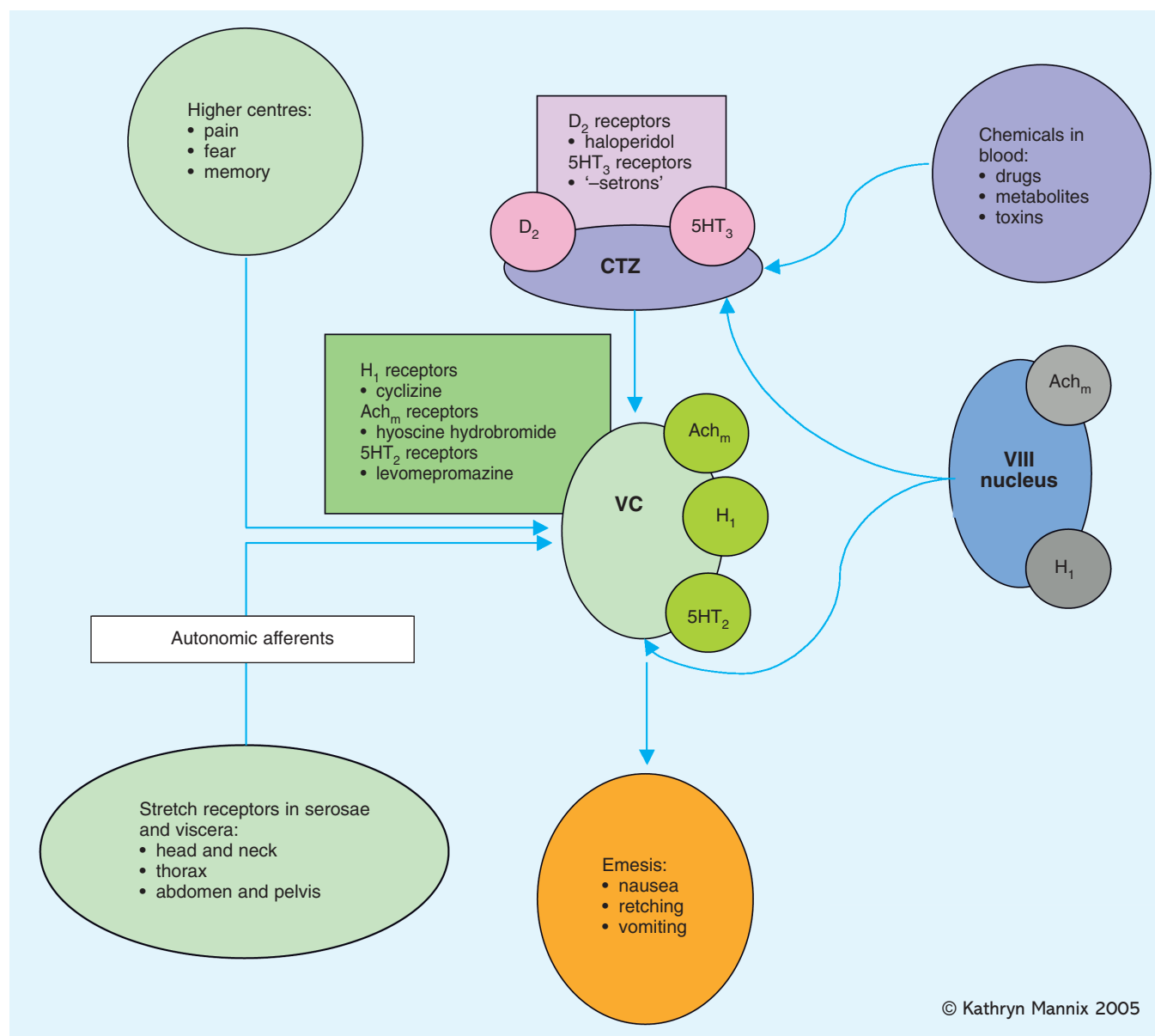


Fig 1. Pathways and neurotransmitters involved in nausea and vomiting. Ach_m = muscarinic acetylcholine receptors; CTZ = chemoreceptor trigger zone; D₂ = dopamine type 2; H₁ = histamine type 1; 5HT₂ and 3 = serotonin receptor subtypes 2 and 3; po = oral; pr = per rectum; sc = subcutaneous; sl = sublingual; TD = transdermal; VC = vomiting centre. Copyright retained by K Mannix.

blood-brain barrier so water-soluble chemicals in blood can diffuse into the cerebrospinal fluid and stimulate the chemoreceptors there.

The vomiting centre (VC) in the brainstem integrates all the components of the reflex, resulting in nausea, salivation, pallor, sweating, retching, protective closure of the glottis and vomiting. The VC receives sensory input from autonomic nerves; stretch receptors on these nerve terminals detect distortion such as liver capsule stretch by metastatic disease, peritoneal distortion by para-aortic lymphadenopathy or bowel dilatation due to obstruction or constipation. Afferents include the vagus, sympathetic trunk and glossopharyngeal nerve. The VC also receives input from higher centres, for example, fear, pain and memory.

Choosing an anti-emetic

With knowledge both of the central pathways that mediate nausea and vomiting and of the neuroreceptors involved, it is possible to select specific receptor antagonist drugs as anti-emetics.⁵ The efficacy of a drug as an anti-emetic is proportional to its binding affinity for its receptor.⁶ The

more selective the binding of a drug, the fewer its side effects. Relative binding affinities are summarised in Table 1.

The eight key steps to successful management of nausea

- 1 *Identify the likely cause(s)* of nausea and/or vomiting: to make an accurate diagnosis of cause(s) requires a thorough assessment including history, examination and diagnostic tests, including biochemistry, infection screen, imaging etc.
- 2 *Identify the pathway* by which each cause triggers the vomiting reflex (Fig 1).
- 3 *Identify the neurotransmitter receptor involved* in each pathway identified.
- 4 *Prescribe the most potent antagonist* to each receptor identified (Table 1). It is usually sufficient to block one receptor at the VC.
- 5 Choose a *route of administration* that ensures the drug will reach its receptors: gastric stasis is usually present in nausea, often precluding the oral route.

- 6 *Give the drug regularly and titrate the dose carefully*, with frequent review of the patient.
- 7 If symptoms persist, *review* all the steps:
 - Is another cause also present, requiring an additional anti-emetic?
 - Is a different cause more likely now that there has been more time to assess the patient?
- 8 Consider whether the trigger can be removed: for example, treat hypercalcaemia, reverse intestinal obstruction and reduce raised intracranial pressure. *Maintain anti-emetics until the trigger is reversed*: if reversal is not possible, long-term anti-emetic therapy may be necessary to maintain palliation.

Other anti-emetic drugs

- *Corticosteroids* are known to have intrinsic anti-emetic action which is not well understood. In addition, their mass-reducing effects may reduce stimulus to nausea in advanced cancer.

Table 1. Receptor binding affinities of commonly used receptor-specific anti-emetic drugs.

Drug	Recommended dose	Receptor binding					
		D ₂ (CTZ)	5HT ₂ (VC)	Ach _m (VC and VIII nucleus)	H ₁ (VC and VIII nucleus)	5HT ₃ (vagal afferent endings)	αAd (antagonists cause hypotension)
Haloperidol	1.5–3 mg daily po or sc	+++	–	–	–	–	–
Metoclopramide	10–20 mg tds po or sc	++	–	–	–	(+)	–
Cyclizine	50 mg tds po or sc	–	–	(+)	+++	–	–
Levomopromazine	6.25–12.5 mg daily po or sc	+	+++	+	+	–	–
Domperidone (does not cross blood-brain barrier)	10–20 mg tds po 30–60 mg tds pr	+	–	–	–	–	–
Prochlorperazine (not recommended)		+	–	+	+	–	+
Hyoscine hydrobromide	400 µg qds sl or sc 500–1,500 µg/72 h TD patch	–	–	+++	–	–	–
Granisetron, ondansetron, etc (not recommended)		–	–	–	–	+++	–

αAd = α-adrenergic; Ach_m = muscarinic acetylcholine receptors; CTZ = chemoreceptor trigger zone; D₂ = dopamine type 2; H₁ = histamine type 1; 5HT₂ and 5HT₃ = serotonin receptor subtypes 2 and 3; po = oral; pr = per rectum; sc = subcutaneous; sl = sublingual; TD = transdermal; VC = vomiting centre.

Clinical examples

1 Bowel obstruction below jejunum

Triggers to nausea:	stretch behind obstruction pain (bowel inflammation and colic) absorption of bacterial toxins	stimulates VC stimulates VC stimulates CTZ
Management:	Establish whether or not surgery or stenting is appropriate: many patients with advanced disease or peritoneal metastases are not candidates for surgery ⁷ and require medical palliation. <i>Cyclizine</i> 50 mg tds sc or per rectum to block VC activity. <i>Haloperidol</i> 1.5–3 mg sc daily in addition, if nausea persists. Once nausea is controlled, oral dosing is effective.	
Consider:	<i>Anticholinergic agents</i> (hyoscine butylbromide 40–120 mg/day or glycopyrrolate 0.1–0.2 mg tds sc) or <i>octreotide</i> 200–1,000 µg/day ⁸ can be used as antisecretory agents and will also relax smooth muscle, thus reducing colic. <i>High-dose corticosteroids</i> may help to reduce pressure and restore patency in malignant bowel obstruction, at least temporarily (eg dexamethasone 12–16 mg daily). ⁹ Correction of dehydration may reduce symptoms. ⁸	

The use of nasogastric tubes and prolonged intravenous fluids is unnecessary; nasogastric tubes may aggravate nausea by glossopharyngeal stimulation and vigorous rehydration will enhance intraluminal secretion of fluid, increasing pressure, colic and nausea.

Patients can eat and drink for pleasure; they should be warned to expect intermittent mechanical vomits, although it should be possible to control nausea.

2 Ureteric obstruction

Triggers to nausea:	ureteric stretch uraemia toxic drug accumulation due to reduced renal clearance	stimulates VC stimulates CTZ stimulates CTZ
Management:	Ureteric stenting will palliate both stretch and chemical stimulation of nausea, but is not always possible. <i>Cyclizine</i> 50 mg tds sc or per rectum to block VC activity. <i>Haloperidol</i> 1.5–3 mg sc daily in addition, if there is renal insufficiency. Doses of renally-excreted drugs will also need to be modified.	

3 Gastric stasis

Gastric emptying may be delayed by anticholinergic drugs, increased intra-abdominal pressure or compression of the gastric outlet.

Symptoms:	Stretching of the stomach by ingested food, drink and air, and by gastric secretions causes distortion of the oesophageal sphincter. This permits acid reflux causing heartburn, whilst the distending stomach irritates the diaphragm causing hiccups. Eating or drinking, even small volumes, when the stomach is already full induces early satiation accompanied by a sensation of bloating. The stomach has great capacity for stretch, and so nausea is not a feature until overstretching occurs; there is often a short period of premonitory nausea, followed by large-volume vomiting which completely relieves all the other symptoms.
Management:	Treatment is most effective when directed at the cause (eg stopping any anticholinergic drugs or tapping ascites). <i>Prokinetic agents</i> (metoclopramide, domperidone) can restore peristalsis and reduce reflux. <i>Proton-pump inhibitors</i> reduce the volume and acidity of gastric secretions. Patients should be encouraged to eat little and often.

In duodenal or high jejunal obstruction, prokinetic drugs may cause colic. The volume of pancreatic and mucosal secretion can be reduced using anticholinergic drugs and/or octreotide (see above); if frequency of vomiting remains intolerable, the use of a venting PEG should be considered for palliation.

CTZ = chemoreceptor trigger zone; PEG = percutaneous endoscopic gastroscopy; sc = subcutaneously; VC = vomiting centre.

- *Serotonin-3 (5HT₃)* receptor antagonists are widely overprescribed. They are effective for early emesis induced by chemotherapy or during radiotherapy across the gastrointestinal tract (eg low thoracic spine, total body irradiation) but probably have no role in other types of nausea caused by cancer. Constipation is a major side effect of this class of drugs.
- *Neurokinin-1 (NK1)* receptor blockers are effective anti-emetics. NK1 receptors are widely distributed in the brain. An oral NK1-receptor antagonist is licensed for use in chemotherapy-induced nausea; its role in palliative care has yet to be explored.

Non-pharmacological measures

Attention should be paid to mood and morale, reducing exposure to strong cooking smells and providing small, palatable meals. Carbohydrate meals are often better tolerated; sour flavours may be preferred by some patients (eg citrus sorbets, lemon drinks).

Psychological techniques to palliate nausea due to advanced disease have not been systematically studied, but studies of relaxation using progressive muscle relaxation and guided mental imagery in chemotherapy patients have shown that the stress of treatment-related nausea can be reduced by these methods.

Acupuncture and *acupressure* have demonstrated useful anti-emetic effects for chemotherapy-related and post-operative nausea and vomiting; the effect of acupuncture can be prolonged by acupressure; *transcutaneous nerve stimulation* at acupuncture points is also effective.^{9,10} There are no studies of acupuncture in a palliative care setting, although individual case reports suggest it can be a successful strategy.

End-of-life care

As the end of life approaches, taking oral medications can be a burden. All the anti-emetics recommended in Table 1 can be given by the sc route. Redness and swelling at the injection site can be a

problem with cyclizine which can be given as a suppository instead. Anticipating the terminal phase and making appropriate adjustments in route of administration of those drugs essential to maintaining comfort are important parts of the cancer team's work. The Liverpool Care Pathway for the dying patient is a national framework for excellent end-of-life care (more information is available from www.lcp-mariecurie.org.uk).

Conclusions

Cancer-related nausea and vomiting may be a presenting symptom of curable disease or a burden of advanced disease. In either case, it is possible to palliate the symptoms by applying a knowledge of the pathways that mediate emesis and selecting anti-emetic drugs on the basis of their site of action. Other disease-modifying treatments, if available, can proceed in parallel with palliation of nausea and vomiting. Good palliation of these distressing symptoms can be achieved and should be the aim of care for nauseated patients.

Conflicts of interest

None.

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Key Points

Nausea and vomiting are common symptoms that can cause enormous misery for cancer patients

It is possible to palliate the symptoms by selecting anti-emetic drugs on the basis of their site of action in the emesis pathway

The efficacy of a drug as an anti-emetic is proportional to its binding affinity for its receptor

The more selective the binding of an anti-emetic drug, the fewer its side effects

The aim of therapy is control of nausea

Choose a non-oral route for anti-emetics until nausea has been absent for 24 hours

5HT₃ receptors have no identified role in palliative care

Medical management of bowel obstruction does not usually include permanent nasogastric intubation or intravenous fluids

Nausea at introduction of opioids occurs in about 30% of patients, but tolerance to nausea arises within two weeks so that anti-emetics can then be withdrawn

KEY WORDS: anti-emetic, bowel obstruction, nausea, palliative treatment, vomiting